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Review Article

Role of cardiorespiratory synchronization and sleep physiology: effects on membrane potential in the restorative functions of sleep

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ABSTRACT

Although sleep physiology has been extensively studied, many of the cellular processes that occur during sleep and the functional significance of sleep remain unclear. The degree of cardiorespiratory synchronization during sleep increases during the progression of slow-wave sleep (SWS). Autonomic nervous system (ANS) activity also assumes a pattern that correlates with the progression of sleep. The ANS is an integral part of physiologic processes that occur during sleep with the respective contribution of parasympathetic and sympathetic activity varying between different sleep stages. In our paper, we attempt to unify the activities of various physiologic systems, namely the cardiac, respiratory, ANS and brain, during sleep into a consolidated picture with particular attention to the membrane potential of neurons. In our unified model, we explore the potential of sleep to promote restorative processes in the brain.

1. Introduction

Although numerous studies have investigated its purpose, a complete picture of the physiologic role of sleep is still unclear. Numerous theories for the primary function of sleep have been proposed, though none have gained sufficient experimental evidence to earn substantial support from the sleep research community [1]. However, many proposed theories restrict the beneficial impact of sleep to specific physiologic processes, which might not allow a complete understanding of the global impact of sleep on the body [2]. It is clear that sleep serves as a restorative function, and the deleterious effects of sleep deprivation are well-documented [3].

Previous studies have established a correlation between neural restoration and sleep regularity. Other forms of restoration in the body also have been observed, but much less evidence supports the notion that sleep provides primarily somatic as opposed to neural restoration [1]. A growing consensus suggests that a major benefit of sleep involves ongoing support for neuronal function in the brain. However, this agreement does not exclude the possibility that other physiologic systems are employed to serve this restorative purpose. For example, cardiorespiratory synchronization that occurs during slow-wave sleep (SWS) in the form of respiratory sinus arrhythmia (RSA) and cardiorespiratory phase synchronization can employ the heart and lungs to assist in the restorative functions of sleep [4]. The degree of synchronization between the heart and lungs may indicate the depth and quality of sleep [5]. This synchronization leads to a shift in the sympathovagal balance during the sleep cycle which can help modulate the membrane potential of neurons, helping to restore optimal function and replenish neurons with crucial supplies for energy [6]. Synchronization also may account for the biologic activity of neurotransmitters and signaling by nuclei of the hypothalamus and brainstem. Future research that focuses on cardiorespiratory synchronization and the modulation of neuronal membrane potential could provide a more accurate model for the function of sleep in both the brain and the body as a whole.

During SWS, membrane potential signaling in the brain is dominated by inhibition, and inhibition has been found to be the biggest contributor to changes in membrane potential. It is likely that inhibition and hyperpolarization processes play an important role during sleep [7]. During SWS, the cortex and subcortical structures like the thalamus, hypothalamus, amygdala, and reticular activating system are globally inhibited and are under strong hyperpolarizing forces [8].

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2. Cardiorespiratory synchronization and autonomic nervous system modulation in sleep

The activities of the heart, respiration, and the autonomic nervous system (ANS) vary between sleep stages [9,10]. The changes in the activity and pattern of these systems are consistent as the stages of sleep progress. Respiration becomes deeper and slower during nonrapid eye movement (NREM) sleep, especially SWS sleep, while breathing becomes more shallow and frequent during rapid eye movement (REM) sleep [11]. Heart rate decreases during NREM sleep and increases throughout periods of REM sleep [12,13]. Reductions in slow spontaneous oscillations in hemodynamics usually present in wakefulness and REM sleep due to increased sympathetic tone also occur during SWS sleep in both cerebral and systemic blood flow [14]. The observed reductions in heart rate, respiration, and blood pressure usually are attributed to a reduction in the metabolic demands of the body and brain [12].

The cyclical changes of the ANS during the sleep cycle accurately reflect those of the heart. During NREM sleep, parasympathetic activity dominates vagal outflow to the heart and body, though REM sleep shows a shift to a more predominate sympathetic influence [5,11,15]. ANS activity is commonly measured during sleep using heart rate variability (HRV) as a noninvasive index of parasympathetic or sympathetic output [16]. A high frequency of variability in beat-to-beat intervals (RR intervals) is indicative of parasympathetic influence on the heart, though low variability coincides with sympathetic activation [17,18]. HRV measurements also can provide a measure of cardiorespiratory synchronization [19].

The concomitant decreases in heart and breathing rates mediate synchronization between heart and respiration. A reduced rate in respiration acts to induce a synchronization of the ANS input and heart rate pattern through activation of the parasympathetic branch of vagus nerve afferents [20–23]. The manifestation of such synchronization is RSA, during which the beat-to-beat intervals of heart rate coincide with respiration [24]. RSA has been shown to continue during sleep states [25]. An additional form of cardiorespiratory coupling provides another measure of the extent of synchronization between the heart and breathing patterns. This form of synchronization is termed *cardiorespiratory phase synchronization* and is defined as breathing cycles and heart beats occurring in the same relative phase for prolonged periods [26,27].

The relationship between cardiorespiratory synchronization and ANS activity during sleep has been well-characterized. Cardiorespiratory phase synchronization coincides with a high level of parasympathetic activity and reaches a plateau during NREM sleep [5,26,28]. In contrast, little to no synchronization occurs during REM sleep [26,28]. Research has shown increasing levels of synchronization throughout NREM sleep with 3 to 1, 4 to 1 (most common), 5 to 1, and even 6 to 1 ratios of cardiac rate to breathing rate during the deepest sleep [28,29]. An increase in various markers of HRV and HRV frequency is closely related to sleep stage progression [30]. This intimate interaction between heart activity and respiration has been observed in individuals of all ages [31–35]. Current evidence from studies examining the impact of slow deep breathing on ANS function suggests that a shift in sympathovagal balance during sleep mediates the synchronization between the heart and lungs [36–39].

In addition, several studies have shown a strong interaction between parasympathetic vagal activity of the heart and the delta and slow waves (electroencephalogram [EEG]) occurring during SWS [33,34,40]. This interaction is believed to be a result of the high frequency of variability in RR intervals during NREM sleep, an indicator of cardiorespiratory synchronization, interacting with delta wave oscillations of the brain [12]. Interestingly, vagal effects on heart rate occur before the observed changes in delta activity during EEG recordings [33,34]. Changes in heart rate and autonomic arousal, measured in relation to RR interval and heart activity, are closely related with EEG measurements during sleep and also precede the corresponding EEG changes [41]. A relationship between EEG and heart activity during sleep also has been shown in infants [42,43]. A recent study found that the interactions of delta EEG activity and cardiorespiratory oscillations during anesthesia primarily are mediated by respiration, followed by corresponding cardiac activity [44]. In agreement, additional evidence demonstrates that neuronal delta oscillations in the olfactory bulb couple with respiratory patterns during breathing in mice [45].

The close relationship between the ANS and sleep can be illustrated by the fact that many medical disorders, such as diabetes mellitus, Alzheimer disease, and Parkinson disease (PD), are associated with both autonomic dysfunction and sleep disorders while some primary sleep disorders are associated with ANS problems [46]. Insights into the importance of cardiorespiratory synchronization during sleep can be gained through the study of sleep apnea, a disorder that impairs breathing. Obstructive sleep apnea (OSA) is marked by the occurrence of regular cessations in breathing that last at least 10 s, but normally 30–60 s, due to the collapse of upper airways during sleep [13]. During apnea episodes, a bradycardia rhythm of the heart occurs followed by a tachycardia at the end of apnea. This pattern has been attributed to parasympathetic control of the heart, interrupted by sympathetic arousal at the end of the apnea [47]. This continuous arousal throughout sleep, though not enough to cause waking, impairs cardiorespiratory synchronization [12,29] and leads to daytime sleepiness from sleep fragmentation [13]. A study by Kabir et al. [29] found that participants with OSA had far less cardiorespiratory synchronization during sleep than those without OSA. We propose that these daytime effects are due in part to the lower levels of synchronized cardiac and respiratory signals that occur, leading to less hyperpolarization and inhibition.

More severe effects of apneas also have been discovered. Research shows that apnea or hypopnea patients have increased levels of sympathetic nerve activity [48], as well as increased risk for cardiovascular disease [49–52]. In addition to apnea sleep disorders, patients who report primary insomnia have reduced cardiorespiratory coupling during sleep and poor sleep quality [53]. Atrial fibrillation, though related to cardiac activity rather than respiration, also impairs sleep. Patients with atrial fibrillation, a common disturbance of normal cardiac rhythm, have been shown to exhibit a significantly poorer quality of sleep compared to control participants [54]. Such a disturbance in the normal heart rhythm likely impairs the amount of cardiorespiratory synchronization possible. In the study [54], correcting the atrial fibrillation and restoring sinus arrhythmia led to an improved sleep quality score, likely due in part to the restoration of cardiorespiratory synchronization. Sleep disorders are common among PD patients [55] and individuals with PD also have been found to experience less cardiorespiratory synchronization than healthy patients [56]. Studies on cardiorespiratory synchronization in patients with other autonomic disorders are lacking, but these studies suggest that some of the restorative effects of sleep may be due to cardiorespiratory synchronization.

Although it is understudied and not well understood, a regular nightly occurrence of cardiorespiratory synchronization and the negative effects correlated with decreased synchronization during sleep suggest an important role for cardiorespiratory synchronization in the function of sleep. Although it may not be the primary function, the observed synchronization between the heart and lungs may provide a means to serve other functions associated with sleep. We suggest that cardiorespiratory synchronization allows the neuronal membrane potential to be regenerated through an autonomic shift towards the parasympathetic state.

3. Effect of cardiorespiratory synchronization on membrane potential

Cardiorespiratory synchronization, that is mediated by respiration during wake and sleep, may lead to widespread homeostatic changes in the membrane potentials of cells. This theory is supported by observations throughout the body (i.e., olfactory bulb, electrical activity of the heart, muscle nerve activity) and also can be applied to sleep states. The effect of respiration and cardiorespiratory synchronization during NREM sleep on the ANS could alter the properties of membrane potentials in target cells. For example, parasympathetic activation leads to the hyperpolarization of the sinoatrial node and ventricular myocardium of the heart [57]. This parasympathetic-induced hyperpolarization leads to a reduction in heart rate. Parasympathetic stimulation becomes the dominant ANS input throughout the body and brain during SWS and can synchronize multiple physiologic processes through the modulation of hemodynamic and blood pressure activity [14,58]. In this way, the ANS can regulate certain forms of homeostasis throughout the body in certain sleep states. Increased parasympathetic activity during cardiorespiratory synchronization and SWS may lead to a general or global hyperpolarization of cellular membrane potential throughout the body. Although this theory is in need of support through research, its possibility is supported by findings by [59] authors who demonstrated that prolonged parasympathetic activation similar to that observed during SWS led to a maintained hyperpolarization of the resting membrane potential of taste cells in frogs [59]. During sleep, the hyperpolarizing activity of cardiorespiratory synchronization and parasympathetic activation may lead to characteristic changes in membrane potential.

4. Membrane potential changes in sleep

Fluctuations in membrane potential that occur during sleep may account for or mediate physiologic activities that occur during sleep. One hypothesis, related to observations of ANS activity during the different sleep stages, might be that the neuronal membrane potential tends to be hyperpolarized during SWS sleep and less polarized during REM and the waking state of consciousness. A recent study involved intracellular recordings of thalamocortical neurons during sleep and demonstrated membrane hyperpolarization during SWS and relative depolarization in REM sleep [60]. Subsequent to this study, additional research has characterized the activity of neurons and their firing patterns during periods of wakefulness and sleep. Intracellular recordings of cortical neurons in mammals have consistently shown a relative depolarized state of membrane potential and increased subthreshold activity during the waking state [61–63]. Observations during REM also exhibit increased neuronal activity. Studies examining the effects of sleep deprivation support these results. Neurons of the rodent prefrontal cortex display increased membrane excitability and increased activity levels following periods of sleep deprivation [64,65]. In addition, the magnitude of hyperpolarization following action potential firing is reduced following sleep deprivation [65]. Increases in prefrontal cortex neuronal excitability and activity levels may contribute to cognitive deficits observed in humans following periods of reduced sleep [66]. This possibility is supported by various studies showing that noise and jitter accumulation due to sustained action potential firing results in impaired action potential precision and communication between neurons [67–70].

Unlike wakefulness or REM sleep, SWS sleep is characterized by the appearance of large amplitude delta waves on EEG. This slow oscillation is caused by thalamocortical neurons alternating between states of depolarized (up) and hyperpolarized (down) membrane potential [71–73]. Such burst firing activity, when sufficiently depolarized in the up state, is in contrast to the constant tonic firing of thalamocortical neurons during the waking state and is achieved through the hyperpolarization of neuronal membrane potential [74]. In addition, a portion of thalamic reticular neurons, thalamic neurons that receive input from the arousal centers of the reticular formation, display a dual stability in their membrane potential [75]. Although this property is intrinsic to the neurons, the intrinsic activity can be modulated by ANS activity and cardiorespiratory synchronization. A transition to a silent more polarized membrane potential state observed during SWS is mediated in response to an experimentally applied hyperpolarizing current. The presence of cardiorespiratory synchronization and parasympathetic activation may modulate the appearance and degree of slow waves by delivering such hyperpolarizing impulses. A recent study showed that the membrane potential of certain populations of cortical neurons is approximately −70 mV during spontaneous SWS and as high as −90 mV during a more profound SWS state induced by ketamine–xylazine [76]. These results suggest a relationship between depth of sleep (i.e., amount of SWS and delta waves) and membrane potential. Fig. 1 illustrates the relative hyperpolarization during the SWS down states in comparison to the relatively depolarized waking state [77]. Other research also suggests these membrane potential changes may be affected by the activity of adjacent glial cells [78,79]. An increase in the overall membrane potential of thalamocortical neurons and neurons in the cortex due to the down states of SWS may serve a restorative function to combat higher membrane excitability and activity during the waking state. This function could be similar to the effects of membrane potential oscillations in the olfactory bulb [80]. A study showed that the presence of a hyperpolarization phase of membrane potential oscillations in olfactory bulb neurons greatly improved action potential precision and stimulus discrimination both in vitro and in vivo. We propose such benefits from hyperpolarizing phases could be extended to neurons throughout the brain, which are hyperpolarized during SWS.

Fig. 2 incorporates the characteristic EEG activity of each sleep stage and membrane potential values of most neurons in each stage. The color spectrum is used to convey different values of membrane potential voltage. The red, purple, and blue portions of the color scale represent relative states of depolarization. The green portion represents a normal resting membrane potential and the yellow indicates a hyperpolarized state of membrane potential. A global mechanism, in which membrane hyperpolarization is induced in multiple cell populations in a synchronized fashion, could provide a functional purpose at a cellular level for sleep and could explain the mechanism through which sleep benefits the brain and other areas of the body.

5. Membrane potential in sleep theories of synaptic plasticity

The impact of cardiorespiratory synchronization on membrane potential, and its possible benefits to revitalization of cellular activity, could be one mechanism through which sleep is beneficial to the body. Numerous mechanisms have been suggested through which sleep promotes central nervous system function. The synaptic renormalization hypothesis, previously termed the *synaptic homeostasis hypothesis,* has garnered much recent attention. This theory suggests that sleep provides an opportunity to prune synapses and strengthen those that are maintained; this process leads to stronger synaptic transmission during awake hours [81,82]. According to this theory, a net increase in synaptic strength occurs during wakefulness but cannot be sustained due to increased energy and space requirements, as well as decreased signal-to-noise ratios of electrical impulses and the resulting neurotransmitter

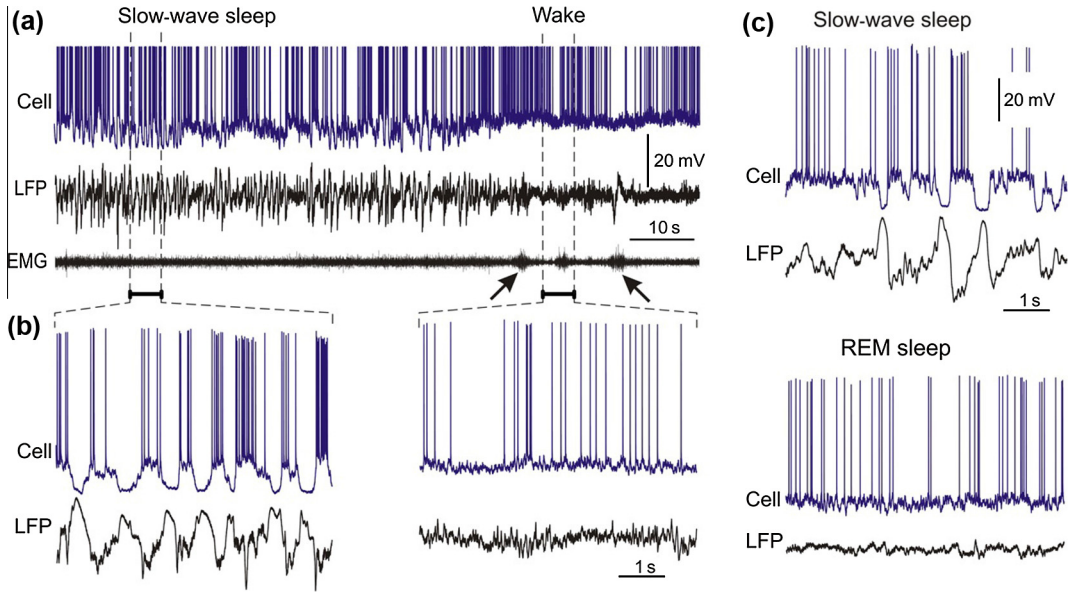

Fig. 1. A view of relative hyperpolarization during slow-wave sleep (SWS) with high cardiorespiratory synchronization and parasympathetic activation recorded from cat neocortical neurons. Local field potential and electromyogram recordings also were recorded (a). Detailed view of up and down states in SWS containing prolonged periods of hyperpolarization and the relative depolarized state during waking periods (b). Reproduced from [77] with permission from copyright holder.

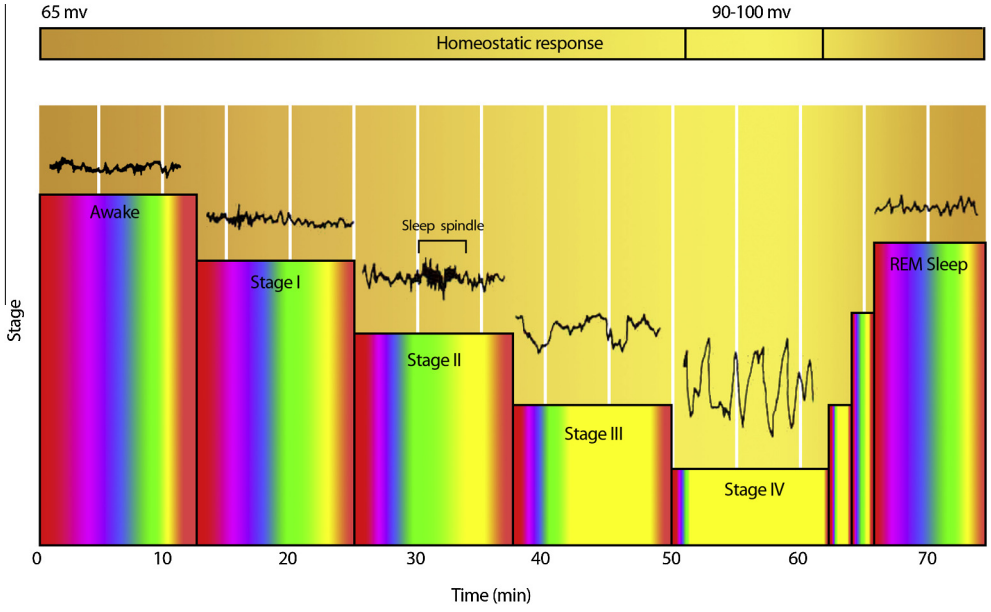

Fig. 2. The electrical activity characteristic of each sleep stage is displayed over the membrane potential activity of neurons in that particular stage. The membrane potential levels are depicted over a spectrum of colors and also are depicted in the trace lines above the bars. A red to blue transition indicates a more depolarized state with green depicting a healthy resting potential. In this depiction, yellow represents a hyperpolarized state. During the waking state the full spectrum is experienced, though neurons are easily depolarized (larger proportion of red, blue purple colors). As sleep progresses into later stages and slow-wave sleep, the membrane potential of neurons becomes progressively hyperpolarized (greater amount of yellow). Rapid eye movement sleep displays a higher proportion of depolarization states similar to that of the waking state. Modified with permission from [144]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

release. This state leads to potentiation, which would result in abnormally low thresholds and altered firing patterns for neurons. Therefore, synaptic renormalization consists of pruning of neurons and allows one to maintain the capacity to learn [83] (for detailed reviews of evidence supporting this theory, see [82,84]). However, current data do not fully explain how membrane potential could provide insight into the basics of the proposed hypothesis. Although evidence exists for the synaptic renormalization theory, some observations seem to contradict its general tenets. Studies have shown increased synaptic strength (i.e., long-term potentiation) during sleep, but generally only in response to learning activities during earlier periods of being awake [85,86]. However, it is important to note that the synaptic renormalization theory suggests a net decrease in synaptic strength due to sleep.

Connecting pieces of evidence for both synaptic upscaling and synaptic renormalization or down-scaling in light of the changes in membrane potential during sleep stages provides evidence for an alternative synaptic embossing theory. This view suggests both synaptic upscaling and downscaling occur during sleep in certain cortical networks [84]. Synaptic renormalization likely occurs in previously nonactivated networks (in absence of novel stimuli) during SWS when neurons are hyperpolarized and relatively

inactive. However, this assumption relies on the idea that SWS is related to synaptic depression [87,88]. On the other hand, synaptic upscaling and strengthening during sleep likely occurs due to the depolarization of neuronal membranes during REM sleep. Indeed most observations of long-term potentiation and synaptic strengthening during sleep in areas associated with previous activation have taken place in REM sleep [89–91]. In general, the effects of sleep on specific synapses likely depend on the stimulation level of the particular brain area, in addition to the neural network containing the synapse [84,92].

6. In relation to sleep neurobiology

Because aspects of sleep and waking are in part governed by the activity of various nuclei and neurotransmitters throughout the brain, this fact should be considered when examining sleep theories. Waking and sleep states are regulated through the interaction of these brain areas through neurotransmitter signals between them. Wakefulness and levels of arousal are dependent on functioning of the reticular formation, a system composed of several small brain regions [93]. Each nucleus or brain area releases excitatory neurotransmitters and reinforces the effects of others through their interactions [94]. The locus coeruleus (LC) is the major supplier of norepinephrine, an excitatory neurotransmitter, and its neurons most often fire during wakefulness, though they are nearly silent during sleep [94]. Levels of LC activity directly correspond to levels of extracellular norepinephrine in the prefrontal cortex [95]. The membrane potentials of neurons in the LC are modulated by respiration and the duration of hyperpolarization has been shown to positively correlate with expiratory interval [96]. This observation suggests that respiration can modulate membrane potentials of neurons. Serotonin is another neurotransmitter involved in arousal and mainly is supplied by the dorsal raphe nucleus, though the tuberomammillary nucleus (TMN) provides histamine during wakefulness. The basal forebrain contains cholinergic neurons that are active during waking and REM sleep but inactive in NREM sleep [97]. The reciprocal connections between each of these arousal systems and efferent connections to other networks in the cortex and thalamus control the state of wakefulness [98]. In addition, several of these nuclei project to the ventrolateral preoptic nucleus (VLPO) of the hypothalamus, which plays a crucial role in sleep [99].

In addition to brainstem regions, the lateral and posterior regions of the hypothalamus have been implicated in the waking states as a supply of excitatory orexin (or hypocretin) neuropeptide [94,100,101]. Orexin-containing neurons in the lateral hypothalamus extensively connect with the previously mentioned arousal areas (i.e., dorsal raphe nucleus, LC, TMN) [102,103]. These regions express orexin receptors and their neurons are activated when exposed to orexin [104–106]. The importance of orexin in regulating arousal levels has been shown in studies of narcolepsy. Human subjects living with narcolepsy routinely display a considerable reduction in the number of orexin neurons, as well as diminished orexin neuropeptide levels in cerebrospinal fluid [107,108]. Sleep–wake cycles also are extensively altered in mice with genetic mutations leading to the knockout of orexin activity [109,110]. In addition, Tsunematsu et al. [111] demonstrated that silencing orexin neurons leads to EEG activity characteristic of SWS. In this study, transgenic mice expressed orexin-positive neurons containing halorhodopsin, which allowed these neurons to be immediately silenced by exposure to orange light. In vivo silencing of the orexin positive neurons with orange light photons led to the slow-wave EEG activity, which characteristic of SWS. Orexin silencing also was accompanied by decreased activity of the serotonin neurons of the dorsal raphe, reinforcing the role of orexin in the regulation of arousal states [111]. Although orexin clearly plays a role in regulating waking and sleep states, it also has been suggested to exert influence over the respiratory and ANS through projections of orexin neurons in the hypothalamus to cardiorespiratory centers of the brainstem [112,113]. Orexin neurons of the lateral hypothalamus also are innervated and inhibited by neurons of the VLPO [103].

Numerous studies have uncovered neuronal populations that are active almost exclusively during sleep. These neurons are mainly located in the VLPO and median preoptic nucleus (MnPO) of the hypothalamus. These nuclei contain neurons using the neurotransmitter gamma-aminobutyric acid (GABA) and fire only during NREM and REM sleep [114–116]. VLPO neurons also make use of the inhibitory neuromodulator galanin [117]. Studies have shown that the VLPO and MnPO contribute to the onset and maintenance of sleep through inhibition of arousal systems (i.e., LC, TMN, dorsal raphe nuclei, lateral and posterior hypothalamus) [98,118–122]. The VLPO and MnPO coordinate their inhibitory activity through reciprocal connections between the two nuclei [122] and also have been implicated in the control of sleep homeostasis [123].

Although no direct correlation has been established through experimental evidence, the modulation of sleep and arousal by these nuclei and networks may be susceptible to cardiorespiratory synchronization during sleep. Interestingly a group of neurons in close proximity to parasympathetic cardiac neurons, important for cardiorespiratory synchronization, are activated during respiration and are GABAergic [124]. These inhibitory neurons may provide a more direct link between cardiorespiratory synchronization and inhibition of arousal systems. In addition, afferent vagal impulses including those relaying cardiac and respiratory information, such as inhibitory impulses from slowly adapting pulmonary stretch receptors, terminate in the brainstem at the nucleus tractus solitarius (NTS) [125,126]. The NTS is known to project to the hypothalamus [127] and it is possible the impulses generated during cardiorespiratory synchronization pronounced in SWS may affect the activity of sleep and arousal nuclei of the brainstem and hypothalamus through NTS projections. Further evidence to support this claim may be found by examining the activity of the NTS during sleep. The NTS has long been implicated in sleep [128–130]. For instance, electrical stimulation of the NTS results in the appearance of EEG activity similar to SWS, though lesions in the NTS lead to paradoxical sleep [128,129]. Inflammation or dysfunction of the NTS also is implicated in OSA, especially in elderly patients [131]. Cardiorespiratory synchronization impulses reaching sleep- and waking-related nuclei through NTS projections may modulate their activity by selectively inhibiting arousal systems. Although more research is needed to substantiate a relationship between cardiorespiratory activity and brain nuclei, the indirect evidence of such a relationship suggests this possibility. While further evidence is needed, the possible role for membrane potential regulation by respiration synchronized cardiac activity and ANS activity during sleep seems to be indirectly supported by several areas of sleep research.

We propose a mechanism regarding NREM SWS in which synchronized cardiorespiratory signals may lead to widespread hyperpolarization and inhibition throughout the brain (Fig. 3). During NREM sleep, the thalamus and cortex become functionally disconnected and decrease in activity [132], though VLPO activity increases in the hypothalamus [115] and hyperpolarizes arousal systems like the reticular activating system [120]. Other areas of the central nervous system such as the amygdala also are inhibited during SWS [133]. We propose that the global increase in cell potentials supports NREM SWS.

We present a REM sleep mechanism in which unsynchronized cardiac and respiratory signals contribute to widespread

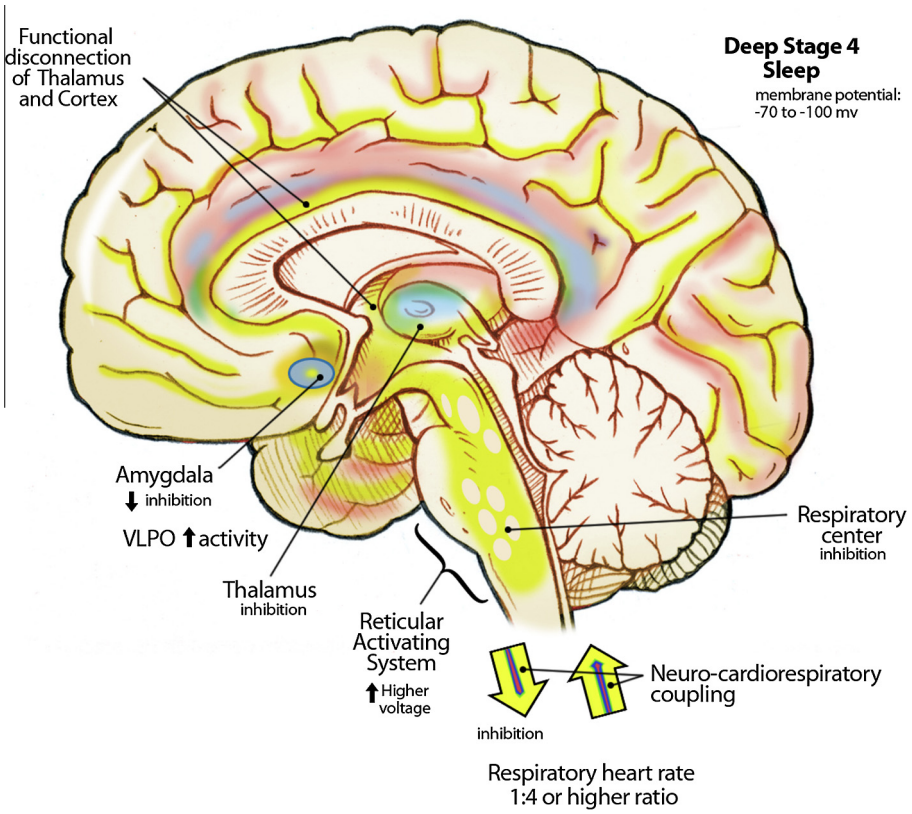

Fig. 3. Overall brain activity during slow-wave sleep. Impulses arising from cardiorespiratory synchronization at a 1 to 4 or higher ratio (predominately yellow arrows) enter the brainstem through vagal afferents. The various nuclei of the reticular activating system are inhibited, partly due to increased activity of the ventrolateral preoptic nucleus. The synchronization and slow-wave behavior of thalamocortical neurons leads to the functional disconnect of the two networks and an overall hyperpolarization of neurons throughout the brain. This hyperpolarization is indicated with yellow shading, consistent with Fig. 2 (Fig. by Mike Jenson MSMI, CMI). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

depolarization (Fig. 4). This depolarization increases activity in many areas of the brain. During REM sleep, activity in the limbic system and respiratory and cardiac centers in the brainstem increase, though the majority of the prefrontal cortex remains at baseline SWS levels [134]. During REM sleep, increased activity in the anterior cingulate, thalamus [135], and VLPO in the hypothalamus occurs, though activity in the posterior cingulate decreases [136]. Acetylcholine levels [97] and amygdala activity increase [137]. The reticular activating system depolarizes and becomes more active [138] and arouses parts of the brain like the thalamus [139]. It has been hypothesized that the major purpose of sleep is to restore the brain [140]. There have not been studies with direct evidence for this restoration hypothesis, but there are many studies concerning the detrimental effects of sleep deprivation that act as indirect evidence [141]. A study by Dworak et al. [142] found that a few hours into SWS there was a two- to three-fold increase in ATP levels in the brain, which then dropped to baseline levels before waking. It is possible that these ATP levels increase more dramatically in areas with high mitochondrial populations and could affect membrane potentials [141]. ATP is required for ATP-dependent transport systems like Na^+/K^+ ATPase that produce hyperpolarizing currents in neurons by moving Na^+ out of cells and K^+ into cells [143]; therefore, it is possible that these increased levels of ATP are used in the process of membrane hyperpolarization and inhibition during SWS.

During NREM sleep cardiorespiratory synchronization is increased by a factor of 2.4 in comparison to wakefulness; however, cardiorespiratory synchronization decreases by a factor of three during REM sleep when compared to wakefulness. This increase in cardiorespiratory synchronization may lead to the widespread hyperpolarization and inhibition, which is followed by the increased levels of ATP that may be used during the inhibition mechanism. It is thought that the decrease in the synchronization of the respiratory and cardiac oscillations during REM sleep is due to disruption by correlated noise produced by the activity of higher brain regions [28].

7. Conclusion

Although it is a daily experience that consumes roughly a third of the human life, the cause and primary function of sleep remain a mysterious topic in science. The predictable changes in EEG recordings, ANS, and other characteristic aspects of physiology occurring during sleep may provide insight into its functions. A focus on the neuroanatomy of sleep has implicated brain regions, such as the reticular formation, the brainstem, the basal forebrain, the hypothalamus, and thalamocortical connections. Various brain neurotransmitter systems also have been shown to play a role in sleep and arousal.

The profound autonomic changes observed during various sleep stages are presently considered peripheral effects of sleep. According to our hypothesis, cardiorespiratory synchronization and corresponding changes in ANS activity, especially during SWS, affect the activity levels of arousal network nuclei and promote the beneficial hyperpolarization of neurons throughout the brain. Although activated during sleep rather than quieted due to hyperpolarization, the preoptic areas of the hypothalamus (VLPO and MnPO) assist in the depression of brain activity and hyperpolarization of other neurons. The proposed mechanism may play a homeostatic role by allowing the regeneration of resting membrane potential and the energy stores of neurons and glia in the brain. Studies are

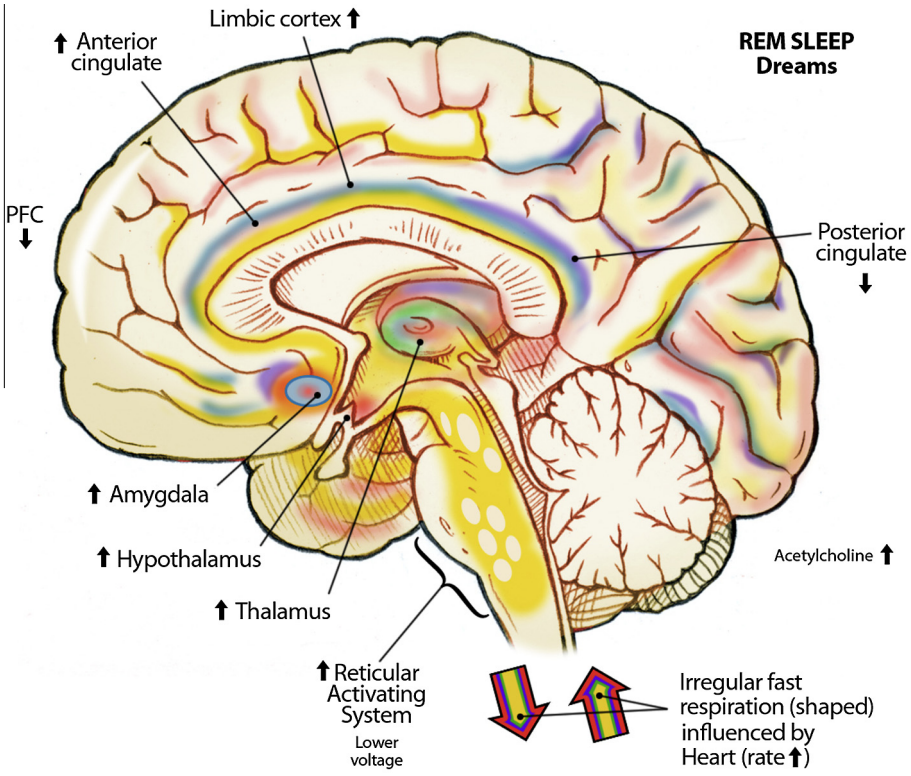

Fig. 4. Brain activity during rapid eye movement sleep. Signals from afferent cardiac and respiratory activity are irregular and indicate depolarized states (arrows indicating these signals are now predominately red). The reticular activating system and other brain regions are slightly depolarized, though not sufficient to produce arousal. Slight depolarization results in the increased cortical activity, which is depicted by blue shading (Fig. by Mike Jenson MSMI, CMI) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

needed to fully elucidate the role of cardiorespiratory synchronization and its associated events in the regulation of neurotransmitter systems and membrane potential during sleep. We anticipate that investigations will establish a central role for cardiorespiratory synchronization and the ANS in the function of sleep. Graded membrane and intracellular potential changes during sleep may prove critical for restoration of electrical and metabolic functions of the brain. Studies on the effects of cardiorespiratory synchronization on neuronal membrane potentials and widespread hyperpolarization and inhibition are lacking and are needed to further understand the dynamics of sleep. A full understanding of sleep physiology is crucial to uncover the principal functions of sleep. Including membrane potential regulation in these proposed mechanisms will contribute insight into the need for and the nature of sleep.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.10.017.

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